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SPOOR AND FISHER

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FORM P.1

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

APPLICATION FOR A PATENT

AND ACKNOWLEDGEMENT OF RECEIPT
(Section 30 (1) – Regulation 22)

The granting of a patent is hereby requested by the undermentioned applicant on the basis of the present application filed in duplicate

OFFICIAL APPLICATION NO.		S AND F REFERENCE
21 01	987425	60197

FULL NAME(S) OF APPLICANT(S)

71 KISSEI PHARMACEUTICAL CO., LTD.

ADDRESS(ES) OF APPLICANT(S)

19-48, YOSHINO, MATSUMOTO-SHI, NAGANO 399, JAPAN

TITLE OF INVENTION

54 PHENYLETHANOLAMINOTETRALIN DERIVATIVES AND BRONCHODILATORS

THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2 THE EARLIEST PRIORITY CLAIM IS:

COUNTRY: JP NUMBER: HEI 9-259233 DATE: 19.08.97

THIS APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO.

21 01

THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND IS BASED ON APPLICATION NO.

21 01

THIS APPLICATION IS ACCOMPANIED BY:

- [x] 1. Two copies of a complete specification of 35 pages.
- [ ] 2. Drawings of ..... sheets.
- [x] 3. Publication particulars and abstract (Form P.8 in duplicate).
- [ ] 4. A copy of Figure ..... of the drawings (if any) for the abstract.
- [x] 5. An assignment of invention.
- [ ] 6. Certified priority document(s) .
- [ ] 7. Translation of the priority document(s).
- [ ] 8. An assignment of priority rights.
- [ ] 9. A copy of the Form P.2 and the specification of S.A. Patent Application No.
- [x] 10. A declaration and power of attorney on Form P.3.
- [ ] 11. Request for ante-dating on Form P.4.
- [ ] 12. Request for classification on Form P.9.
- [ ] 13.

74 ADDRESS FOR SERVICE: SPOOR AND FISHER, SANDTON

Dated: 18 AUGUST 1998

SPOOR AND FISHER
PATENT ATTORNEYS FOR THE APPLICANT(S)

RECEIVED

REGISTRAR OF PATENTS, TRADE MARKS AND COPYRIGHT

1998 -08- 18

REGISTRAR OF PATENTS
REGISTRATEUR VAN PATENTE, HANDELSMERKE EN OUTEURSREG

SPOOR AND FISHER

FORM P.7
(To be lodged in duplicate)

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

COMPLETE SPECIFICATION

(Section 30(1) – Regulation 28)

OFFICIAL APPLICATION NO.		LODGING DATE	
21 01	987425	22	18.08.98

INTERNATIONAL CLASSIFICATION	
51	C07C

FULL NAME(S) OF APPLICANT(S)	
71	KISSEI PHARMACEUTICAL CO., LTD.

FULL NAME(S) OF INVENTOR(S)	
72	TETSURO TAMAI; NOBUYUKI TANAKA; HIDEYUKI MURANAKA; KEN KIKUCHI; NAOYUKI TSUTSUMI; MASUO AKAHANE

TITLE OF INVENTION	
54	PHENYLETHANOLAMINOTETRALIN DERIVATIVES AND BRONCHODILATORS

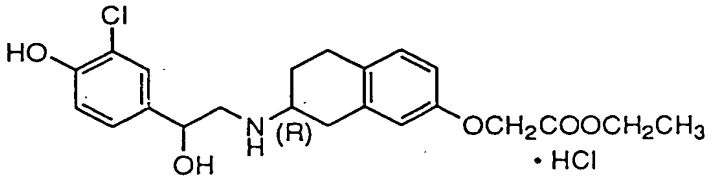
DESCRIPTION

Technical Field

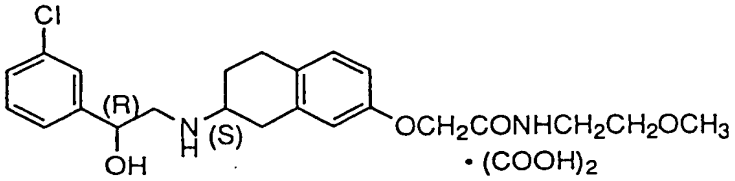
The present invention relates to novel phenylethanolaminotetralin derivatives and pharmaceutically acceptable salts thereof which are useful as medicaments.

Background Art

As substituted phenylethanolaminotetralin derivatives, compounds having gut selective sympathomimetic and anti-pollakiuria activities have been disclosed, e.g., a compound represented by the formula:



(wherein the carbon atom marked with (R) represents a carbon atom in (*R*) configuration) and a compound represented by the formula:



(wherein the carbon atom marked with (S) represents a carbon atom in (*S*) configuration; and the carbon atom marked with (R) has the same meaning as defined above) (cf. a published Japanese patent application (*kohyo*) No. Hei 6-506676 and a published

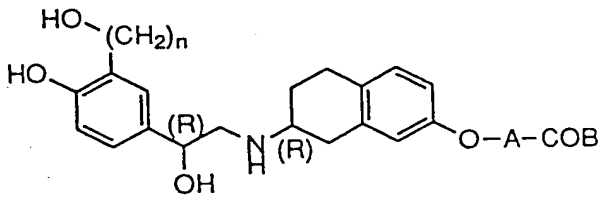
Japanese patent application (*kohyo*) No. Hei 6-506955).

However, these compounds are β_3-adrenergic receptor-stimulating agents having remarkable β_3-adrenergic receptor-stimulating activity.

Disclosure of Invention

The present inventors have extensively studied in order to find compounds which are useful as bronchodilators. As a result, it has been found that certain phenylethanolamino-tetralin derivatives wherein the phenyl moiety is substituted at the 3- and 4-positions and the tetralin moiety is substituted by a carbamoylalkoxy group at the 7-position have a potent and selective bronchodilating activity, and therefore are very useful as bronchodilators, thereby forming the basis of the present invention.

Accordingly, the present invention relates to phenylethanolaminotetralin derivatives represented by the general formula:



(I)

(wherein A represents a lower alkylene group; B represents an amino group, a di(lower alkyl)amino group or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom in the ring chain; n is an integer of 1 or 2; and the carbon atoms marked

with (R) represent carbon atoms in (*R*) configuration) and pharmaceutically acceptable salts thereof.

The present invention relates to a pharmaceutical composition comprising the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof.

The present invention relates to a bronchodilator which comprises, as the active ingredient, the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof.

The present invention relates to a method for the prevention or treatment of bronchial asthma which comprises administering the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof.

The present invention relates to a use of the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for the prevention or treatment of bronchial asthma.

The present invention relates to a use of the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof as bronchodilator.

The present invention relates to a process for the manufacture of a pharmaceutical composition for the prevention

or treatment of bronchial asthma, characterized in the use, as an essential constituent of said pharmaceutical composition, of the phenylethanolaminotetralin derivative represented by the above general formula (I) or pharmaceutically acceptable salt thereof.

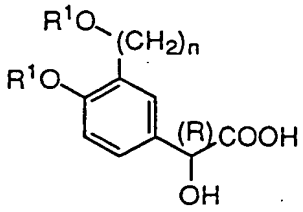
In the compounds represented by the above general formula (I) of the present invention, the term "di(lower alkyl)amino group" means an amino group disubstituted by different or same straight- or branched-chain alkyl groups having from 1 to 6 carbon atoms such as a methyl group, an ethyl group, a propyl group, an isopropyl group and the like, and as examples of such a group, a dimethylamino group, a diethylamino group, an ethylmethylamino group and the like can be illustrated.

The term "lower alkylene group" means a straight-chain alkylene group having from 1 to 3 carbon atoms such as a methylene group, an ethylene group and a trimethylene group.

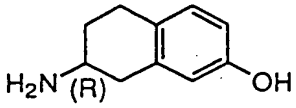
As examples of a 3- to 7-membered alicyclic amino group which may contain an oxygen atom in the ring chain, a 1-pyrrolidinyl group, a piperidino group, a morpholino group and the like can be illustrated.

The compounds represented by the above general formula (I) of the present invention can be prepared by the following methods.

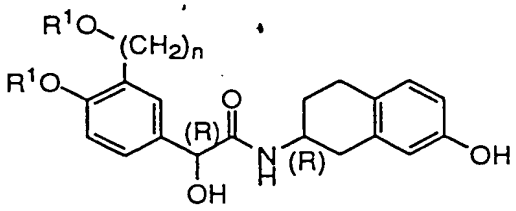
The compounds represented by the above general formula (I) of the present invention, for example, can be prepared by allowing an optically active mandelic acid derivative represented by the general formula:


(II)

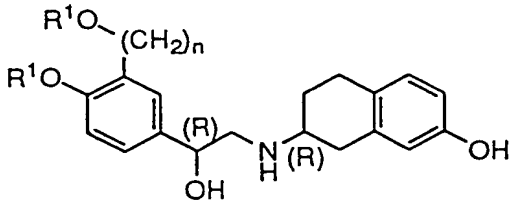
(wherein R^1 represents a hydroxy-protective group; and n and the carbon atom marked with (R) have the same meanings as defined above) to react with an optically active amine compound represented by the formula:


(III)

(wherein the carbon atom marked with (R) has the same meaning as defined above) in the presence of a condensing agent to give a single isomer represented by the general formula:


(IV)

(wherein R^1, n and the carbon atoms marked with (R) have the same meanings as defined above), reducing the resulting compound using a reagent such as borane-dimethylsulfide complex to prepare a single isomer represented by the general formula:


(V)

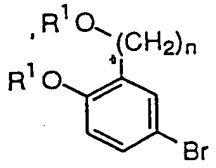
(wherein R^1, n and the carbon atoms marked with (R) have the same meanings as defined above), protecting the alcoholic hydroxy

group and amino group with a reagent such as trifluoroacetic anhydride as occasion demands, subjecting the resulting phenolic compound to *O*-alkylation using an alkylating agent represented by the general formula:

$$X\text{-}A\text{-}COB \qquad (VI)$$

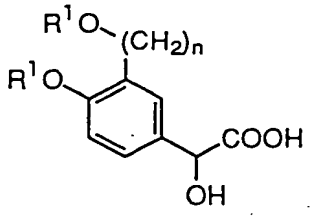
(wherein X represents a halogen atom; and A and B have the same meanings as defined above), and removing the protective group.

The optically active mandelic acid compounds represented by the above general formula (II) which are used as starting materials in the above production process can be prepared by treating a phenyl bromide derivative represented by the general formula:



(VII)

(wherein R^1 and n have the same meanings as defined above), which can be obtained according to methods described in literatures or analogous processes thereto, with an alkyl lithium, allowing the resulting phenyl lithium derivative to react with diethyl oxalate, reducing the resulting phenylglyoxylic acid derivative using a reagent such as sodium borohydride, and hydrolyzing the ester compound to give a mandelic acid derivative represented by the general formula:



(VIII)

(wherein R^1 and n have the same meanings as defined above) and subjecting the compound to optical resolution in the usual way using a resolving agent such as optically active 1-(1-naphthyl)-ethylamine.

The amine compound represented by the above formula (III) which is used as starting material in the above production process can be prepared according to methods described in literatures or analogous methods thereto (e.g., *Eur. J. Med. Chem.*, Vol. 29, 259-267 (1994); a published Japanese patent application (*Kokai*) No. Hei 3-14548).

The compounds of the present invention obtained by the above production process can be easily isolated and purified by conventional separation means such as fractional recrystallization, purification using column chromatography, solvent extraction and the like.

The phenylethanolaminotetralin derivatives represented by the above general formula (I) of the present invention can be converted into their pharmaceutically acceptable salts in the usual way. Examples of such salts include acid addition salts with mineral acids (e.g., hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like), acid addition salts with organic acids (e.g., formic

acid, acetic acid, menthoxyacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, glutamic acid, aspartic acid and the like) and salts with inorganic bases such as a sodium salt and a potassium salt.

In addition, the compounds represented by the above general formula (I) of the present invention also include its hydrates and solvates with pharmaceutically acceptable solvents (e.g., ethanol).

When the *in vitro* test for measuring bronchodilating activity (β_2-adrenergic receptor-stimulating effect) was carried out in the usual way using isolated guinea-pig trachea as described below, for example, the Compound 1 described in Example 1 showed a 50 % relaxing activity on tracheal smooth muscle contraction induced by a molar concentration of 1.0×10^{-5} of histamine (EC_{50} value) at a molar concentration of 2.5×10^{-10}, and the Compound 2 described in Example 2 showed the EC_{50} value at a molar concentration of 5.0×10^{-9}. Thus, the compounds of the present invention are excellent compounds having markedly potent bronchodilating activity.

When the *in vitro* test for measuring an activity to the heart (β_1-adrenergic receptor-stimulating effect) was carried out in the usual way using isolated guinea-pig atrium as described below, the Compound 1 described in Example 1 showed an activity

to increase 20 beats per minute of heart rate ($EC_{\Delta 20}$ value) at a molar concentration of 7.8×10^{-9}, and the Compound 2 described in Example 2 showed the $EC_{\Delta 20}$ value at a molar concentration of 6.6×10^{-8}. Thus, the compounds of the present invention have markedly weaker activity to the heart (β_1-adrenergic receptor-stimulating effect) in comparison with the above bronchodilating activity (β_2-adrenergic receptor-stimulating effect).

In consequence, the compounds of the present invention have markedly potent bronchodilating activity and weakened activity to the heart such as tachycardia, so that these are extremely useful as potent and selective bronchodilators of in which burdens on the heart are reduced.

Also, the compounds represented by the above general formula (I) of the present invention are extremely stable compounds and therefore have excellent storage stability.

When the phenylethanolaminotetralin derivatives represented by the above general formula (I) of the present invention and pharmaceutically acceptable salts thereof are employed in the practical treatment, they are administered orally or parenterally in the form of appropriate pharmaceutical compositions such as tablets, powders, fine granules, granules, capsules, inhalations, injections and the like. These pharmaceutical compositions can be formulated in accordance with conventional methods using conventional pharmaceutical carriers, excipients and other additives.

The dosage is appropriately decided depending on the sex,

age, body weight, degree of symptoms and the like of each patient to be treated, which is approximately within the range of from 1 to 1,000 mg per day per adult human in the case of oral administration and approximately within the range of from 0.01 to 100 mg per day per adult human in the case of parenteral administration such as injections, and the daily dose can be divided into one to several doses per day. The dosage is approximately within the range of from 0.05 to 500 mg per day per adult human in the case of inhalations.

Best Mode for Carrying Out the Invention

The present invention is further illustrated in more detail by way of the following Reference Examples, Examples and Test Examples. The present invention is not limited thereto.

Reference Example 1

(+)-(2*R*)-2-(2,2-Dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide

To a stirred solution of 6-bromo-2,2-dimethylbenzo-[1,2-d]-1,3-dioxane (30.0 g) in tetrahydrofuran (610 ml) was added 1.56 M n-butyl lithium in hexane (136 ml) at -80°C under an argon atmosphere, and the mixture was stirred for 15 minutes. After the reaction mixture was added to a stirred solution of diethyl oxalate (21.6 g) in tetrahydrofuran (200 ml) at -80°C under an argon atmosphere, the mixture was stirred for an hour,

and ethanol (100 ml) and a solution of sodium borohydride (1.40 g) in ethanol (100 ml) were sequentially added to the reaction mixture. After the mixture was stirred for 30 minutes at -30°C, acetic acid (8.26 ml) was added to the reaction mixture, and the resulting mixture was additionally stirred for 5 minutes. To the reaction mixture was added a solution of potassium bicarbonate (14.8 g) in water (50 ml), and the mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 5/1) gave ethyl 2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetate (25.1 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.24 (3H, t, J=7.1Hz), 1.54 (6H, s), 3.39 (1H, d, J=5.6Hz), 4.10-4.35 (2H, m), 4.84 (2H, s), 5.06 (1H, d, J=5.6Hz), 6.80 (1H, d, J=8.4Hz), 7.03 (1H, d, J=1.9Hz), 7.19 (1H, dd, J=8.4, 1.9Hz)

To a stirred solution of ethyl 2-(2,2-dimethylbenzo-[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetate (78.3 g) in ethanol (145 ml) was added 2 N aqueous sodium hydroxide solution (176 ml) under ice-cooling. After the mixture was stirred for 1.5 hours at room temperature, 2 N aqueous sulfuric acid solution (174 ml) was added to the reaction mixture under ice-cooling with stirring. The mixture was diluted with water and brine, and

extracted with ethyl acetate. The extract was washed with brine and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. The residue and (*R*)-(+)-1-(1-naphthyl)-ethylamine (50.3 g) were dissolved in ethanol (210 ml) and the solution was allowed to stand at room temperature to give precipitates (48.3 g). Recrystallization of the precipitates from ethanol (88 ml) gave 1:1:1 salt (43.6 g) of (-)-(*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetic acid, (*R*)-(+)-1-(1-naphthyl)ethylamine and ethanol having a melting point of 164-165°C.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.15-1.30 (9H, m), 1.38 (3H, s), 3.70 (2H, q, J=7.0Hz), 4.15 (1H, s), 4.38 (1H, d, J=15.2Hz), 4.49 (1H, d, J=15.2Hz), 4.71 (1H, q, J=6.7Hz), 6.46 (1H, d, J=8.4Hz), 6.53 (1H, d, J=1.8Hz), 6.61 (1H, dd, J=8.4, 1.8Hz), 7.30-7.45 (2H, m), 7.50-7.65 (2H, m), 7.75 (1H, d, J=8.4Hz), 7.84 (1H, d, J=7.9Hz), 7.91 (1H, d, J=8.1Hz)

Specific rotation: $[\alpha]_D^{25}$ = -33.7° (c=0.52, CH_3OH)

To a stirred suspension of 1:1:1 salt (43.6 g) of (-)-(*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetic acid, (*R*)-(+)-1-(1-naphthyl)ethylamine and ethanol in water (200 ml) and ethyl acetate (300 ml) was added 2 N aqueous sulfuric acid solution (47.9 ml) under ice-cooling. After the mixture was stirred for 30 minutes, the reaction mixture was filtered through a pad of Celite®, the organic layer separated from the filtrate was washed with water and dried over anhydrous

magnesium sulfate, and the solvent was removed *in vacuo*. Recrystallization of the residue from ethyl acetate-diisopropyl ether gave (-)-(*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetic acid (22.8 g) having a melting point of 115-118°C (decomposition).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.45 (6H, s), 4.81 (2H, s), 4.92 (1H, s), 5.30-6.00 (1H, br), 6.75 (1H, d, J=8.4Hz), 7.09 (1H, d, J=1.8Hz), 7.18 (1H, dd, J=8.4, 1.8Hz), 12.50 (1H, br)

Specific rotation: $[\alpha]_D^{25}$ = -113.3° (c=1.54, CH_3CN)

To a stirred solution of (-)-(*R*)-2-(2,2-dimethylbenzo-[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyacetic acid (5.2 g), (*R*)-2-amino-7-hydroxytetralin hydrobromide (5.4 g) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (10.2 g) in *N,N*-dimethylformamide (100 ml) was added triethylamine (9.2 ml) at room temperature, and the mixture was stirred for 14 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 1/2) gave (+)-(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (7.4 g) as an amorphous.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.60 (6H, m), 1.65-1.80 (1H, m),

2.00-2.10 (1H, m), 2.54 (1H, dd, J=16.2, 8.1Hz), 2.70-2.90 (2H, m), 3.00 (1H, dd, J=16.2, 5.0Hz), 3.30 (1H, d, J=3.4Hz), 4.20-4.30 (1H, m), 4.82 (2H, s), 4.88 (1H, s), 4.95 (1H, d, J=3.4Hz), 6.15 (1H, d, J=8.3Hz), 6.48 (1H, d, J=2.6Hz), 6.62 (1H, dd, J=8.1, 2.6Hz), 6.81 (1H, d, J=8.4Hz), 6.94 (1H, d, J=8.1Hz), 7.00 (1H, br s), 7.16 (1H, dd, J=8.4, 1.9Hz)

Specific rotation: $[\alpha]_D^{25}$ = +9.1° (c=0.53, CH_3OH)

Reference Example 2

(+)-2-[(2*R*)-2-[[(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide

To a stirred solution of (+)-(2*R*)-2-(2,2-dimethyl-benzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (7.4 g) in tetrahydrofuran (100 ml) was added 10 M borane-dimethylsulfide complex (4.4 ml) at room temperature, and the mixture was heated under reflux for 4 hours. After cooling, a solution of triethanolamine (11.5 g) in tetrahydrofuran (20 ml) was added to the reaction mixture at room temperature, and the resulting mixture was heated under reflux for 35 hours. After cooling, the solvent was removed *in vacuo* and the residue was diluted with water. The resulting mixture was extracted with ethyl acetate, the extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. The residue was dissolved in tetrahydrofuran (100 ml), and to the

solution were added 5 N aqueous sodium hydroxide solution (7.7 ml) and 2-bromo-*N*,*N*-dimethylacetamide (4.2 g) under ice-cooling with stirring. After the mixture was stirred for 2 hours, diethylamine (2.0 ml) was added to the reaction mixture at room temperature with stirring and the mixture was stirred for an hour. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. Precipitation of the residue from 30:1 ethyl acetate-ethanol (20 ml) gave (+)-2-[(2*R*)-2-[[(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydro-naphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (4.29 g) as an amorphous.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.70 (7H, m), 2.00-2.15 (1H, m), 2.50-3.20 (13H, m), 4.60 (1H, dd, J=9.2, 3.5Hz), 4.64 (2H, s), 4.85 (2H, s), 6.65 (1H, d, J=2.6Hz), 6.74 (1H, dd, J=8.3, 2.6Hz), 6.80 (1H, d, J=8.4Hz), 6.95-7.05 (2H, m), 7.14 (1H, dd, J=8.4, 2.3Hz)

Specific rotation: $[\alpha]_D^{25}$ = +28.7° (c=0.30, CH_3OH)

Reference Example 3

(+)-4-[2-[(2*R*)-2-[[(2*R*)-2-(2,2-Dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydro-naphthalen-7-yloxy]acetyl]morpholine

(+)-4-[2-[(2*R*)-2-[[(2*R*)-2-(2,2-Dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydro-

naphthalen-7-yloxy]acetyl]morpholine as an amorphous was prepared according to a similar manner to that described in Reference Example 2 using 4-(2-bromoacetyl)morpholine instead of 2-bromo-*N*,*N*-dimethylacetamide.

^{1}H-NMR (DMSO-d_6) δ ppm: 1.45 (6H, s), 1.60-1.75 (1H, m), 1.85-2.00 (1H, m), 2.35-2.95 (7H, m), 3.40-3.65 (8H, m), 4.50-4.60 (1H, m), 4.72 (2H, s), 4.75-4.85 (2H, m), 5.17 (1H, d, J=4.1Hz), 6.61 (1H, d, J=2.5Hz), 6.65 (1H, dd, J=8.3, 2.5Hz), 6.72 (1H, d, J=8.3HZ), 6.94 (1H, d, J=8.3Hz), 7.04 (1H, s), 7.13 (1H, d, J=8.3Hz)

Specific rotation: $[\alpha]_D^{29}$ = +27.5° (c=1.07, CH_3OH)

Reference Example 4

(-)-(2*R*)-2-[4-Benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide

To a stirred suspension of benzyl [2-(2-benzyloxyethyl)phenyl] ether (159 mg) and sodium acetate (123 mg) in acetic acid (2 ml) was added bromine (29 μ l) at room temperature. After the mixture was stirred for an hour, a solution of sodium sulfite heptahydrate (100 mg) in water (20 ml) was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water, a saturated aqueous sodium bicarbonate solution and water sequentially, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column

chromatography on silica gel (eluent: hexane/methylene chloride = 2/1) gave benzyl [2-(2-benzyloxyethyl)-4-bromophenyl] ether (173 mg) as an oil.

^{1}H-NMR ($CDCl_3$) δ ppm: 2.97 (2H, t, J=7.0Hz), 3.68 (2H, t, J=7.0Hz), 4.50 (2H, s), 5.02 (2H, s), 6.75 (1H, d, J=8.7Hz), 7.20-7.40 (12H, m)

To a stirred solution of benzyl [2-(2-benzyloxyethyl)-4-bromophenyl] ether (24.0 g) in tetrahydrofuran (200 ml) was added 1.57 M n-butyl lithium in hexane (47.0 ml) at -95°C under an argon atmosphere, and the mixture was stirred for 15 minutes. After the reaction mixture was added to a stirred solution of diethyl oxalate (10.8 g) in tetrahydrofuran (300 ml) at -95°C under an argon atmosphere, the mixture was stirred for an hour, and ethanol (200 ml) and sodium borohydride (755 mg) were sequentially added to the reaction mixture. After the mixture was stirred for 45 minutes at -35°C, acetic acid (4.70 ml) was added to the reaction mixture, and the resulting mixture was additionally stirred for 15 minutes. To the reaction mixture was added a solution of sodium bicarbonate (6.9 g) in water (300 ml), and the mixture was concentrated *in vacuo*. The residue was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: hexane/ethyl acetate = 3/1) gave ethyl 2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-

hydroxyacetate (19.9 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.21 (3H, t, J=7.1Hz), 3.02 (2H, t, J=7.3Hz), 3.34 (1H, d, J=5.9Hz), 3.70 (2H, t, J=7.3Hz), 4.10-4.30 (2H, m), 4.51 (2H, s), 5.05 (2H, s), 5.08 (1H, d, J=5.9Hz), 6.87 (1H, d, J=8.4Hz), 7.20-7.40 (12H, m)

To a stirred suspension of ethyl 2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetate (39.7 g) in ethanol (40 ml) was added 2 N aqueous sodium hydroxide solution (57 ml) under ice-cooling. After the mixture was stirred for an hour at room temperature, 2 N aqueous sulfuric acid solution (57 ml) was added to the reaction mixture under ice-cooling with stirring, and the resulting mixture was extracted with ethyl acetate. The extract was washed with water and dried over anhydrous magnesium sulfate. Concentration of the extract gave 2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid (35.1 g) as an oil.

^{1}H-NMR ($CDCl_3$) δ ppm: 3.01 (2H, t, J=7.1Hz), 3.71 (2H, t, J=7.1Hz), 4.50 (2H, s), 5.06 (2H, s), 5.16 (1H, s), 6.89 (1H, d, J=8.4Hz), 7.20-7.40 (12H, m)

2-[4-Benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid (16.31 g) and D-phenylalaninol (6.29 g) were dissolved in ethanol (23 ml) by heating. The solution was allowed to stand for 16 hours at room temperature, and the resulting precipitates were collected by filtration. Recrystallization of the precipitates from ethanol gave salt (6.36 g) of (*R*)-

2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid and D-phenylalaninol. The salt (2.71 g) of (*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid and D-phenylalaninol was suspended in water (10 ml) and ethyl acetate (15 ml), and to the suspension was added 1 N aqueous sulfuric acid solution (5.0 ml) under ice-cooling with stirring. After the mixture was stirred for 30 minutes, the organic layer separated was washed with brine and dried over anhydrous magnesium sulfate. Concentration *in vacuo* of the extract gave (*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid (2.21 g).

^{1}H-NMR ($CDCl_3$) δ ppm: 3.01 (2H, t, J=7.1Hz), 3.71 (2H, t, J=7.1Hz), 4.50 (2H, s), 5.06 (2H, s), 5.16 (1H, s), 6.89 (1H, d, J=8.4Hz), 7.20-7.40 (12H, m)

To a stirred solution of (*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyacetic acid (2.21 g), (*R*)-2-amino-7-hydroxytetralin hydrobromide (1.22 g) and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (2.20 g) in *N*,*N*-dimethylformamide (10 ml) was added triethylamine (1.39 ml) at room temperature. After the mixture was stirred for 12 hours, the reaction mixture was diluted with ethyl acetate, and the mixture was washed with water and a saturated aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid

column chromatography on silica gel (eluent: methylene chloride/ethyl acetate = 1/1) gave (-)-(2*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (2.01 g).

^{1}H-NMR ($CDCl_3$) δ ppm: 1.65-1.75 (1H, m), 1.90-2.05 (1H, m), 2.45-2.55 (1H, m), 2.70-2.80 (2H, m), 2.90-3.05 (3H, m), 3.49 (1H, d, J=3.2Hz), 3.70 (2H, t, J=7.1Hz), 4.15-4.30 (1H, m), 4.50 (2H, s), 4.93 (1H, d, J=3.4Hz), 5.04 (2H, s), 5.63 (1H, br s), 6.29 (1H, d, J=8.2Hz), 6.41 (1H, d, J=2.7Hz), 6.59 (1H, dd, J=8.2, 2.7Hz), 6.85 (1H, d, J=8.2Hz), 6.90 (1H, d, J=8.3Hz), 7.15-7.40 (11H, m)

Specific rotation: $[\alpha]_D^{31} = -10.7°$ (c=0.73, $CHCl_3$)

Reference Example 5

(+)-2-[(2*R*)-2-[[(2*R*)-2-[4-Benzyloxy-3-(2-benzyloxyethyl)-phenyl]-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide

To a stirred solution of (-)-(2*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxy-*N*-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)acetamide (1.95 g) in tetrahydrofuran (20 ml) was added 10 M borane-dimethylsulfide complex (1.23 ml) at room temperature, and the mixture was heated under reflux for 3 hours. After cooling, a solution of triethanolamine (3.06 g) in tetrahydrofuran (3 ml) was added to the reaction mixture, and the mixture was heated under reflux for 6 hours . After cooling, the reaction mixture was concentrated *in vacuo* and the residue

was diluted with ethyl acetate. The resulting mixture was washed with water and brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on silica gel (eluent: methylene chloride/methanol = 2/1) gave (+)-(1*R*)-1-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)ethanol (1.10 g).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.35-1.50 (1H, m), 1.60-1.70 (1H, m), 1.85-2.00 (1H, m), 2.30-2.95 (8H, m), 3.62 (2H, t, J=7.2Hz), 4.45-4.55 (3H, m), 5.09 (2H, s),5.15 (1H, d, J=4.2Hz), 6.42 (1H, d, J=2.6Hz), 6.48 (1H, dd, J=8.2, 2.6Hz), 6.82 (1H, d, J=8.2Hz), 6.97 (1H, d, J=8.5Hz), 7.15 (1H, dd, J=8.5, 2.1Hz), 7.19 (1H, d, J=2.1Hz), 7.20-7.45 (10H, m), 8.97 (1H, s)

Specific rotation: $[\alpha]_D^{30}$ = +28.7° (c=0.78, CH_3OH)

To a stirred solution of (+)-(1*R*)-1-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-((2*R*)-7-hydroxy-1,2,3,4-tetrahydronaphthalen-2-ylamino)ethanol (1.08 g) in tetrahydrofuran (12 ml) were added 5 N aqueous sodium hydroxide solution (936 μ l) and 2-bromo-*N*,*N*-dimethylacetamide (505 mg) at room temperature. After the mixture was stirred for 2 hours, diethylamine (315 μ l) was added to the reaction mixture at room temperature, and the mixture was additionally stirred for 30 minutes followed by dilution with water and then extraction with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. Purification of the residue

by medium pressure liquid column chromatography on aminopropyl silica gel (eluent: methylene chloride/methanol = 50/1) gave (+)-2-[(2*R*)-2-[[(2*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)-phenyl]-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (1.18 g).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.40-1.55 (1H, m), 1.60-1.75 (1H, m), 1.85-2.00 (1H, m), 2.35-3.00 (14H, m), 3.62 (2H, t, J=7.1Hz), 4.46 (2H, s), 4.50-4.60 (1H, m), 4.69 (2H, s), 5.09 (2H, s), 5.16 (1H, d, J=4.2Hz), 6.58 (1H, d, J=2.5Hz), 6.64 (1H, dd, J=8.4, 2.5Hz), 6.93 (1H, d, J=8.4Hz), 6.97 (1H, d, J=8.3Hz), 7.15 (1H, dd, J=8.3, 2.1Hz), 7.20 (1H, d, J=2.1Hz), 7.20-7.45 (10H, m)

Specific rotation: $[\alpha]_D^{29}$ = +24.2° (c=3.01, CH_3OH)

Example 1

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (Compound 1)

To a stirred solution of (+)-2-[(2*R*)-2-[[(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (4.8 g) in tetrahydrofuran (50 ml) was added 1 N hydrochloric acid (50 ml) under ice-cooling. After the mixture was stirred for 2 hours, 1 N aqueous sodium hydroxide solution (50 ml) was added to the reaction mixture under ice-cooling with stirring, and the resulting mixture was concentrated to dryness *in vacuo*. After the residue was diluted with methylene chloride, the

insoluble material was filtrated off and the filtrate was concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on aminopropyl silica gel (eluent: methylene chloride/methanol = 15/1) gave (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (3.2 g) as an amorphous. Crystallization of the amorphous from ethanol gave solids having a melting point of 95-98°C.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.45-1.65 (1H, m), 1.90-2.05 (1H, m), 2.35-2.50 (1H, m), 2.60-2.90 (6H, m), 2.96 (3H, s), 3.06 (3H, s), 4.51 (1H, dd, J=8.8, 3.7Hz), 4.61 (2H, s), 4.67 (2H, s), 6.56 (1H, d, J=2.5Hz), 6.67 (1H, dd, J=8.4, 2.5Hz), 6.75 (1H, d, J=8.3Hz), 6.90-7.00 (2H, m), 7.04 (1H, dd, J=8.3, 1.8Hz)

Specific rotation: $[\alpha]_D^{31}$ = +30.7° (c=1.07, CH_3OH)

Example 2

(+)-4-[2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine (Compound 2)

(+)-4-[2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]acetyl]morpholine as an amorphous was prepared according to a similar manner to that described in Example 1 using (+)-4-[2-[(2*R*)-2-[[(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-

tetrahydronaphthalen-7-yloxy]acetyl]morpholine instead of (+)-2-[(2*R*)-2-[[(2*R*)-2-(2,2-dimethylbenzo[1,2-d]-1,3-dioxan-6-yl)-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide.

^{1}H-NMR (DMSO-d_6) δ ppm: 1.40-1.55 (1H, m), 1.65 (1H, br), 1.85-2.00 (1H, m), 2.35-2.50 (1H, m), 2.55-2.95 (6H, m), 3.40-3.65 (8H, m), 4.40-4.55 (3H, m), 4.72 (2H, s), 4.80-5.15 (2H, m), 6.62 (1H, d, J=2.7Hz), 6.65 (1H, dd, J=8.3, 2.7Hz), 6.69 (1H, d, J=8.2Hz), 6.94 (1H, d, J=8.3Hz), 7.01 (1H, dd, J=8.2, 2.1Hz), 7.27 (1H, d, J=2.1Hz), 9.15 (1H, br)

Specific rotation: $[\alpha]_D^{29}$ = +28.3° (c=1.59, CH_3OH)

Example 3

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hemifumarate (Compound 3)

To a solution of (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (154 mg) in ethanol (10 ml) was added fumaric acid (22 mg), and the mixture was heated until it was homogeneous. After cooling, collection of the precipitates by filtration gave (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hemifumarate (153 mg) having a melting point of 174-177°C (decomposition).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.50-1.65 (1H, m), 2.00-2.15 (1H, m), 2.50-3.10 (13H, m), 4.47 (2H, s), 4.60-4.75 (3H, m), 4.95 (1H, br), 6.46 (1H, s), 6.60-6.70 (2H, m), 6.72 (1H, d, J=8.3Hz), 6.95 (1H, d, J=8.3Hz), 7.04 (1H, dd, J=8.3, 2.1Hz), 7.30 (1H, d, J=2.1Hz), 9.25 (1H, br)

Specific rotation: $[\alpha]_D^{31}$ = +19.6° (c=0.48, H_2O)

Example 4

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hemisulfate (Compound 4)

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-(4-hydroxy-3-hydroxymethylphenyl)ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hemisulfate having a melting point of 155-158°C was prepared according to a similar manner to that described in Example 3 using 0.5 N aqueous sulfuric acid solution instead of fumaric acid.

^{1}H-NMR (DMSO-d_6) δ ppm: 1.60-1.75 (1H, m), 2.15-2.30 (1H, m), 2.60-3.20 (12H, m), 3.25-3.40 (1H, m), 4.49 (2H, s), 4.71 (2H, s), 4.83 (1H, dd, J=9.7, 2.8Hz), 5.00 (1H, br), 6.65 (1H, d, J=2.6Hz), 6.68 (1H, dd, J=8.4, 2.6Hz), 6.76 (1H, d, J=8.2Hz), 6.97 (1H, d, J=8.4Hz), 7.08 (1H, dd, J=8.2, 2.1Hz), 7.34 (1H, d, J=2.1Hz), 9.35 (1H, br)

Specific rotation: $[\alpha]_D^{31}$ = +21.6° (c=0.51, H_2O)

Example 5

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (Compound 5)

A suspension of (+)-2-[(2*R*)-2-[[(2*R*)-2-[4-benzyloxy-3-(2-benzyloxyethyl)phenyl]-2-hydroxyethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (1.10 g) and 10% palladium on activated carbon (55 mg) in acetic acid (10 ml) was stirred for 16 hours at room temperature under a hydrogen atmosphere. After the reaction mixture was filtrated to remove the catalyst, the filtrate was concentrated *in vacuo*. Purification of the residue by medium pressure liquid column chromatography on aminopropyl silica gel (eluent: methylene chloride/methanol = 10/1) gave (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (702 mg).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.35-1.70 (2H, m), 1.85-2.00 (1H, m), 2.35-3.00 (14H, m), 3.50-3.60 (2H, m), 4.40-4.50 (1H, m), 4.69 (2H, s), 5.05 (1H, d, J=3.8Hz), 6.59 (1H, d, J=2.7Hz), 6.63 (1H, dd, J=8.3, 2.7Hz), 6.70 (1H, d, J=8.1Hz), 6.93 (1H, d, J=8.3Hz), 6.98 (1H, dd, J=8.1, 2.1Hz), 7.03 (1H, br s), 9.10 (1H, br)

Specific rotation: $[\alpha]_D^{30}$ = +23.2° (c=0.56, CH_3OH)

Example 6

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-

yloxy]-*N*,*N*-dimethylacetamide hemifumarate (Compound 6)

To a solution of (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide (2.0 g) in ethanol (10 ml) was added fumaric acid (271 mg), and the mixture was heated until it was homogeneous. After cooling, collection of the precipitates by filtration gave (+)-2-[(2*R*)-2-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]-amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethyl-acetamide hemifumarate (1.3 g) having a melting point of 185-187°C (decomposition).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.50-1.65 (1H, m), 2.00-2.15 (1H, m), 2.55-3.15 (15H, m), 3.55 (1H, t, J=7.4Hz), 4.55-4.65 (1H, m), 4.71 (1H, s), 6.46 (1H, s), 6.62 (1H, d, J=2.5Hz), 6.66 (1H, dd, J=8.4, 2.5Hz), 6.74 (1H, d, J=8.2Hz), 6.96 (1H, d, J=8.4Hz), 7.01 (1H, dd, J=8.2, 1.9Hz), 7.07 (1H, d, J=1.9Hz)

Specific rotation: $[\alpha]_D^{23}$ = +20.4° (c=0.49, H_2O)

Example 7

The following compounds were prepared according to a similar manner to that described in Example 6 using the corresponding acids instead of fumaric acid.

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxy-ethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hemisulfate (Compound 7)

^{1}H-NMR (DMSO-d_6) δ ppm: 1.50-1.70 (1H, m), 2.05-2.20 (1H, m), 2.60-3.50 (17H, m), 3.56 (2H, t, J=7.2Hz), 4.60-4.75 (3H, m), 6.63 (1H, d, J=2.5Hz), 6.67 (1H, dd, J=8.4, 2.5Hz), 6.75 (1H, d, J=8.2Hz), 6.96 (1H, d, J=8.4Hz), 7.03 (1H, dd, J=8.2, 2.0Hz), 7.09 (1H, d, J=2.0Hz), 9.20 (1H, br)

Specific rotation: $[\alpha]_D^{23}$ = +29.3° (c=0.49, CH_3OH)

Melting point: 172-174°C (decomposition) (recrystallization solvent: CH_3CH_2OH)

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hydrochloride (Compound 8)

^{1}H-NMR (DMSO-d_6) δ ppm: 1.65-1.80 (1H, m), 2.25-2.35 (1H, m), 2.60-3.20 (14H, m), 3.35-3.65 (3H, m), 4.65-4.90 (4H, m), 5.99 (1H, br s), 6.67 (1H, d, J=2.6Hz), 6.71 (1H, dd, J=8.4, 2.6Hz), 6.80 (1H, d, J=8.2Hz), 6.99 (1H, d, J=8.4Hz), 7.06 (1H, dd, J=8.2, 2.1Hz), 7.12 (1H, d, J=2.1Hz), 8.70 (1H, br), 9.25 (1H, br), 9.40 (1H, s)

Specific rotation: $[\alpha]_D^{23}$ = +26.4° (c=0.53, CH_3OH)

Melting point: 193-195°C (decomposition) (recrystallization solvent: CH_3CH_2OH)

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide hydrobromide (Compound 9)

^{1}H-NMR (DMSO-d_6) δ ppm: 1.65-1.80 (1H, m), 2.25-2.35 (1H, m),

2.60-2.95 (8H, m), 2.98 (3H, s), 3.05-3.20 (2H, m), 3.25-3.55 (2H, m), 3.57 (2H, t, J=7.3Hz), 4.65-4.85 (4H, m), 6.00 (1H, br s), 6.68 (1H, d, J=2.3Hz), 6.71 (1H, dd, J=8.3, 2.3Hz), 6.79 (1H, d, J=8.2Hz), 7.00 (1H, d, J=8.3Hz), 7.07 (1H, dd, J=8.2, 1.9Hz), 7.13 (1H, d, J=1.9Hz), 8.65 (1H, br), 8.80 (1H, br), 9.37 (1H, s)

Specific rotation: $[\alpha]_D^{23}$ = +24.1° (c=0.52, CH_3OH)

Melting point: 194-195°C (decomposition) (recrystallization solvent: CH_3CH_2OH)

(+)-2-[(2*R*)-2-[[(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yloxy]-*N*,*N*-dimethylacetamide D-tartrate (Compound 10)

^{1}H-NMR (DMSO-d_6) δ ppm: 1.60-1.75 (1H, m), 2.20-2.30 (1H, m), 2.60-2.90 (8H, m), 2.95-3.15 (6H, m), 3.30-3.40 (1H, m), 3.56 (2H, t, J=7.3Hz), 3.95 (2H, s) , 4.70-4.80 (3H, m), 6.66 (1H, d, J=2.6Hz), 6.69 (1H, dd, J=8.4, 2.6Hz), 6.77 (1H, d, J=8.2Hz), 6.98 (1H, d, J=8.4Hz), 7.06 (1H, dd, J=8.2, 2.1Hz), 7.11 (1H, d, J=2.1Hz)

Specific rotation: $[\alpha]_D^{23}$ = +26.4° (c=0.51, H_2O)

Melting point: 120-122°C (recrystallization solvent: CH_3CH_2OH)

Test Example 1

Action of drugs to isolated guinea-pig trachea

Male Hartley guinea-pigs (450-600 g in body weight) were killed by exanguination and the tracheae were isolated. To

obtain the strip chain preparation, 4 or 5 tracheal chains were tied together with threads. The preparation was suspended in a Magnus bath containing a Krebs-Henseleit solution at 37°C aerated with a mixture gas containing 95% of oxygen and 5% of carbon dioxide, and 1 g of load was applied. The change in tension was measured with a force-displacement transducer and the response was recorded on a rectigram. The relaxant effect of drug was investigated on histamine (10^{-5} M)-induced contraction by the cumulative addition of this drug. The 100% of the relaxation was expressed as a maximal relaxation induced by 10^{-5} M forskolin, and the EC_{50} value was defined as the concentration of drug that caused 50% of the maximal response.

Compound	EC_{50} Value (M)
1	2.5×10^{-10}
2	5.0×10^{-9}
5	8.0×10^{-10}

Test Example 2

Action of drugs to isolated atrium

Atria of male Hartley guinea-pigs (450 to 600 g in body weight) were isolated and the test was carried out in accordance with the Magnus method. The sample was suspended in a Krebs-Henseleit solution at 37°C aerated with a mixture gas containing 95% of oxygen and 5% of carbon dioxide, and 0.5 g of load was applied. The spontaneous motility was measured with a force-

displacement transducer and the response was recorded on a rectigram. After addition of drug, its efficacy was evaluated by calculating $EC_{\Delta 20}$ value, which is the drug concentration that increases 20 beats per minute of heart rate.

Compound	$EC_{\Delta 20}$ Value (M)
1	7.8×10^{-9}
2	6.6×10^{-8}

Test Example 3

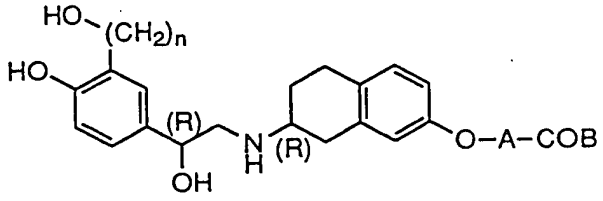
Acute toxicity test

A compound was administered intravenously to male ICR mice (5 weeks old) at prescribed doses. During 24 hours after the administration, it was observed and judged whether there is dead mouse.

Compound	Dose (mg/kg)	The Number of Deaths
1	20	0 / 5
2	30	0 / 5
5	40	0 / 5

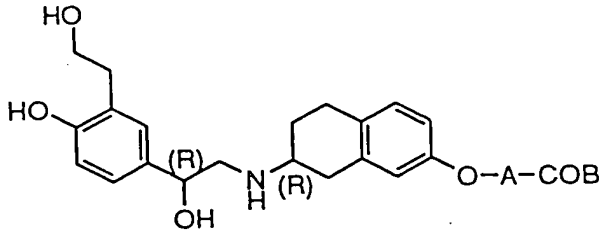
CLAIMS

1. A phenylethanolaminotetralin derivative represented by the general formula:



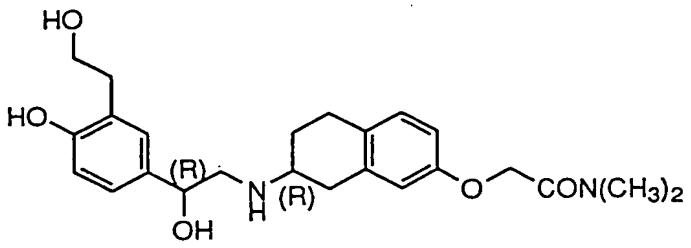
(wherein A represents a lower alkylene group; B represents an amino group, a di(lower alkyl)amino group or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom in the ring chain; n is an integer of 1 or 2; and the carbon atoms marked with (R) represent carbon atoms in (*R*) configuration) and pharmaceutically acceptable salt thereof.

2. A phenylethanolaminotetralin derivative as claimed in claim 1, represented by the general formula:



(wherein A represents a lower alkylene group; B represents an amino group, a di(lower alkyl)amino group or a 3 to 7-membered alicyclic amino group which may contain an oxygen atom in the ring chain; and the carbon atoms marked with (R) represent carbon atoms in (*R*) configuration) and pharmaceutically acceptable salt thereof.

3. The phenylethanolaminotetralin derivative as claimed in claim 2, represented by the formula:



(wherein the carbon atoms marked with (R) represent carbon atoms in (*R*) configuration) and pharmaceutically acceptable salt thereof.

4. A pharmaceutical composition comprising the phenylethanolaminotetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims 1, 2 or 3.

5. A bronchodilator which comprises, as the active ingredient, the phenylethanolaminotetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims 1, 2 or 3.

6. A phenylethanolamino-tetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims 1, 2 or 3 for use in a method for the prevention or treatment of bronchial asthma.

7. A use of the phenylethanolaminotetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims

1, 2 or 3 for the manufacture of a pharmaceutical composition for the prevention or treatment of bronchial asthma.

8. A use of the phenylethanolaminotetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims 1, 2 or 3 as a bronchodilator.

9. A process for the manufacture of a pharmaceutical composition for the prevention or treatment of bronchial asthma, characterized in the use, as an essential constituent of said pharmaceutical composition, of the phenylethanolaminotetralin derivative or pharmaceutically acceptable salt thereof as claimed in claims 1, 2 or 3.

10. A compound according to claim 1 as specifically described herein.

DATED THIS 18TH DAY OF AUGUST 1998

SPOOR AND FISHER
APPLICANTS PATENT ATTORNEYS